Bicyclic and Tricyclic Ergoline Partial Structures. Rigid 3-(2-Aminoethyl)pyrroles and 3- and 4-(2-Aminoethyl)pyrazoles as Dopamine Agonists

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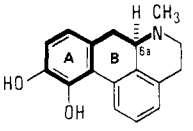
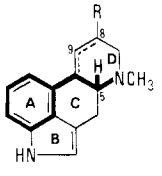
It is proposed, based upon comparisons with apomorphine, that the rigid pyrroleethylamine moiety of the ergolines is the portion of the molecule responsible for dopamine agonist activity. In support of this hypothesis, bicyclic and tricyclic ergoline partial structures **6**, **11**, **25**, and **35** have been synthesized. In addition, some pyrazole isosters (**37**, **38**, **40**, and **45**) of these rigid pyrroleethylamines have been made. *All* of the classes show dopaminergic activity in prolactin inhibition and in lesioned rat turning assays. The most potent drugs, the linear tricyclic pyrazoles **38** (R = Pr) and **40** (R = Pr), are comparable in potency with the highly active ergoline pergolide (**41**).

In recent years dopamine agonist drugs have seen a remarkable growth in therapeutic utility.[1] Although apomorphine, the prototype drug, has found use mainly as an emetic, more recently other dopamine agonists have been shown to be potent inhibitors of release of the pituitary hormone prolactin.[1] Because of this property, certain ergoline derivatives, such as bromocryptine (2-bromo-α-ergokryptin) and lergotrile (2-chloro-6-methylergoline-8β-acetonitrile), have been found useful in the inhibition of postpartum lactation[1] and have been dramatically effective in the treatment of the galactorrhea-amenorrhea syndrome.[1] A further development has been the application of these drugs in acromegaly,[1] and most recently both bromocriptine and lergotrile have shown promise in the dopamine-deficiency disease parkinsonism.[1] Since the clinical use of apomorphine is limited by poor oral absorption and short duration of action, the advent of the ergolines as dopamine agonists has been a significant advance.

When one considers the mode of action and active moiety of dopamine agonist drugs, one focuses attention first on apomorphine (**1a**), the classical drug of this group. In this instance, it is now well established by the thorough work of Cannon[2] and others[3] that the active moiety of the molecule is the rigid dopamine portion, as shown in **1a**.

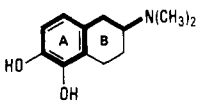


1a



2a

Apomorphine is of the *R* absolute configuration at carbon-6a[4] as indicated, and the corresponding *S* enantiomer is *inactive*.[5] In attempts to elucidate the active site, Cannon prepared the apomorphine AB partial structure **3** ("M7")[2] and found it to be very comparable in activity to apomorphine itself. Other studies have confirmed that the unique rigid dopamine portion is the important part

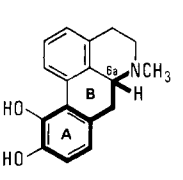


3

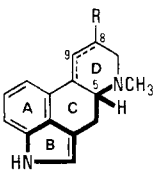
of the apomorphine molecule.[3]

On the other hand, when one examines the structure of the ergolines (**2a**), it is not obvious as to which portion of the molecule confers dopamine agonist properties. This question is compounded by the fact that the ergolines show many pharmacological properties other than dopamine agonism (5-HT antagonism, α-blocking activity, vasoconstriction, oxytocic action, hallucinogenic effects, etc.). Nevertheless, some have assumed that the rigid β-phenethylamine portion of the ergolines, as shown in **2a**, is the active moiety responsible for the dopamine agonist properties of this class.[6] On closer inspection, however, this assumption is not supported. The natural ergolines (**2a**) also have the *R* absolute configuration at carbon atom 5[7] as shown, and once again the opposite *S* enantiomers are known to be inactive.[8] Obviously, the stereochemistry is critically important. If one examines structures **1a** and **2a**, it is seen that the hydrogen atoms at C6a and C5, respectively, in the corresponding fragments, are of *opposite configuration*. Therefore, it would appear highly unlikely that the rigid phenethylamine portion of ergoline (**2a**) would correspond to the rigid dopamine in apomorphine (**1a**). In fact, it would be the *inactive, unnatural* (*S*)-ergoline which would correspond to the *active, natural* (*R*)-apomorphine if the two β-aminotetralin portions were compared.

However, if the two molecules are rewritten as in **1b** and **2b**, an alternative mode of comparison is evident. In this



1b



2b

pair it is apparent that it is now the rigid *pyrroleethylamine* portion of **2b** which corresponds with the rigid dopamine in **1b**. In this analogy the hydrogen atoms at C5 and C6a, respectively, are now of the *same* configuration. Thus, as a working hypothesis, we suggest that the

(1) P. F. Spano and M. Trabucci, Eds., *Pharmacology*, **16** (Suppl. 1), 1–213 (1978); B. Hökfelt and S. J. Nillius, Eds., *Acta Endocrinol. (Copenhagen), Suppl.*, **no. 216**, 1–227 (1978).
(2) J. G. Cannon, J. C. Kim, and M. A. Aleem, *J. Med. Chem.*, **15**, 348 (1972).
(3) D. D. Miller, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 2392 (1978); J. L. Neumeyer, W. P. Dafeldecker, B. Costall, and R. J. Naylor, *J. Med. Chem.*, **20**, 190 (1977); J. L. Neumeyer, B. R. Neustadt, K. H. Oh, K. K. Weinhardt, C. B. Boyce, F. J. Rosenberg, and D. G. Teiger, *ibid.*, **16**, 1223 (1973).
(4) J. Giesecke, *Acta Crystallogr., Sect. B*, **33**, 302 (1977).
(5) W. S. Saari, S. W. King, and V. J. Lotti, *J. Med. Chem.*, **16**, 171 (1973).
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(8) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 944 (1943).

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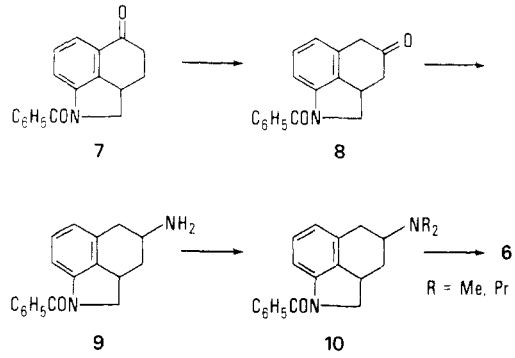
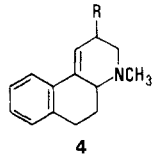
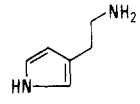
Scheme I



moiety in the ergoline class which is responsible for dopamine agonist properties is the *rigid pyrroleethylamine* rather than the phenethylamine. Nichols[9] has independently and elegantly advanced this same suggestion. In order to experimentally test this hypothesis, we describe in this paper the synthesis and biological evaluation of several bicyclic and tricyclic ergoline partial structures, each of which contains the pyrroleethylamine moiety. In addition, we report some pyrazole analogues of the partial structures. It is of interest to note at this point that most of the previous work[10] on ergoline partial structures has resulted in compounds, e.g., analogue **4**,[11] in which the rigid pyrroleethylamine moiety has been either discarded or disrupted. Little of biological interest has been the result.

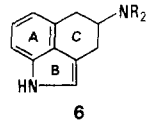


Chemistry. Our first task was to prepare and evaluate 3-(2-aminoethyl)pyrrole (**5**). This compound was prepared

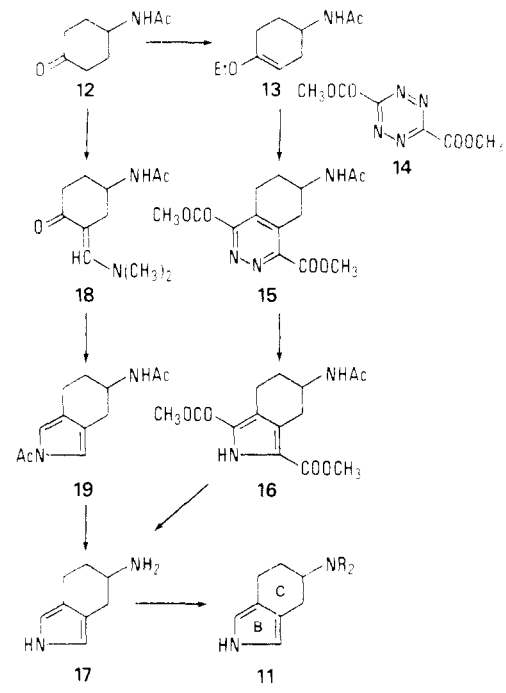


by the method of Osanova and Piskov[12] and was evaluated as the maleate salt. In reserpinized male rats, **5** was *ineffective* in lowering prolactin.[26] Dopamine agonists (apomorphine and numerous ergolines) invariably show good lowering of prolactin in this assay. However, in this *acute* test dopamine itself is likewise *inactive*, probably because of rapid inactivation by monoamine oxidase. The amine **5** doubtless also would be subject to a similar rapid degradation. The rest of our work, therefore, centered about the study of more stable, *rigid tertiary* amines.

ABC Tricyclic Ergoline Partial Structures. The ABC tricyclic ergoline partial structures **6** (R = CH_3 or H),



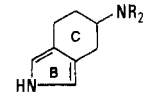
Scheme II



in which ring D of the ergoline system is lacking, were reported previously by Stoll and Petrzilka[13] and by Harris and Uhle.[14] However, an evaluation of the dopamine agonist properties of these compounds has not been available. We prepared this class by a new route, as shown in Scheme I.

The tricyclic ketone **7**, which we had used in our total synthesis of lysergic acid,[15] was converted to the β-tetralone **8** as previously described,[15] or better, by a modification of Nichols' recent improved procedure.[16] Reductive amination of the ketone **8** with ammonium acetate and $NaCNBH_3$ afforded the primary amine **9**, which was converted to the tertiary amines **10** via formaldehyde or propionaldehyde and $NaCNBH_3$. Conversion of **10** to **6** was then effected by acid hydrolysis and MnO_2 oxidation. Biological evaluation of compounds **6** (R = Me, Pr) showed that they were indeed active in our dopamine agonist tests (see below). However, these results did not shed much light on the pyrroleethylamine hypothesis above, since compounds **6**, like the ergolines, contain *both* a rigid β-phenethylamine portion and a pyrroleethylamine moiety *together* in the same molecule. We turned, therefore, to an examination of partial structures in which this ambiguity did not exist.

BC Bicyclic Ergoline Partial Structures. The rigid bicyclic pyrrole derivative **11** contains rings B and C of the



ergoline system and a tertiary amine function in the requisite position. It relates to an ergoline in the same

(9) D. E. Nichols, *J. Theor. Biol.*, **59**, 167 (1976).
(10) E. Campaigne and D. R. Knapp, *J. Pharm. Sci.*, **60**, 809 (1971).
(11) H. G. Leemann and S. Fabri, *Helv. Chim. Acta*, **42**, 2696 (1959); J. C. Craig, D. M. Temple, and B. Moore, *Aust. J. Chem.*, **14**, 84 (1961); Z. Horii, T. Watanabe, T. Kurihara, and Y. Tamura, *Chem. Pharm. Bull.*, **13**, 420 (1965).
(12) L. K. Osanova and V. B. Piskov, *Sint. Prior. Soedin., Ikh Analogov Fragm.*, 208 (1965); *Chem. Abstr.*, **65**, 5432a (1966).
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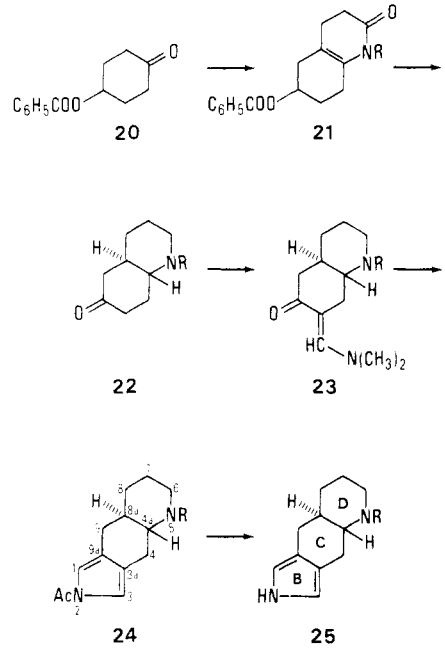
(14) L. S. Harris and F. C. Uhle, *J. Pharmacol. Exp. Ther.*, **128**, 358 (1960).
(15) E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, and R. B. Woodward, *J. Am. Chem. Soc.*, **78**, 3087 (1956).
(16) D. E. Nichols, J. M. Robinson, G. S. Li, J. M. Cassady, and H. G. Floss, *Org. Prep. Proced. Int.*, **9**, 277 (1977).

Scheme III



fashion as **3** ("M7") relates to apomorphine. We prepared **11** by two methods, as summarized in Scheme II.

4-Acetamidocyclohexanone (**12**)[17] was converted to the enol ether **13**, and this in turn was condensed in a Diels–Alder reaction with 1,2,4,5-tetrazinedicarboxylic ester (**14**)[18] to give the pyridazine diester **15**. Structure **15** on treatment with zinc and acetic acid[19] underwent reductive ring contraction to the pyrrole diester **16**. Removal of the extraneous ester and amide groups of **16** was accomplished by hydrolysis and decarboxylation to yield the bicyclic pyrroleethylamine **17**.

A superior route to **17** involved condensation of 4-acetamidocyclohexanone (**12**) with dimethylformamide dimethyl acetal to yield the enamino ketone **18**. Base-catalyzed reaction of **18** with glycine, according to the procedure of Zav'yalov et al.,[20] afforded an adduct, which on treatment with acetic anhydride was cyclized, decarboxylated, and acetylated to give the diamide **19**. Basic hydrolysis of **19** produced the primary amine, **17**, which with acetaldehyde or propionaldehyde and $NaCNBH_3$ gave the tertiary amines **11** (R = Et and Pr). This Russian pyrrole synthesis[20] proved to be very general and was equally useful in the synthesis of the following BCD tricyclic partial structures.

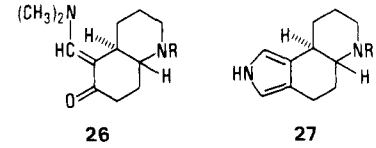
BCD Tricyclic Ergoline Partial Structures. The route to the linear BCD tricyclic series (which lacks only the benzene ring of the ergolines) is shown in Scheme III. Our plan in this case was to construct a suitable octahydro-6(2*H*)-quinolinone (**22**) and then employ the above synthesis of Zav'yalov et al.[20] to build on the requisite pyrrole ring. The first objective was accomplished using a standard quinoline synthesis[21] by converting 4-(benzoyloxy)cyclohexanone (**20**)[22] to its pyrrolidine enamine.

Table I. ^{13}C NMR Peak Assignments (ppm) of Tricyclic Compound **24** (R = $CH_2C_6H_5$), Maleate Salt

167.8	Ac*C*O	114.0	3 or 1
167.3	maleate *C*O	64.1	4a
135.6	maleate =*C*	55.7	Ar*C*H_2
131.3	3,5-Ar	51.4	6
130.2	1-Ar	36.0	8a
129.3	4-Ar	29.3	9
128.8	2,6-Ar	28.1	8
121.8	9a or 3a	24.7	4
120.7	9a or 3a	21.9	Ac*C*H_3, 7
115.1	1 or 3		

This on reaction with acrylamide gave the hexahydro-2-(1*H*)-quinolinone **21** (R = H). Subsequently, **21** (R = H) was converted to the required cyclohexanone **22** in the following five steps: (a) alkylation of the nitrogen, (b) $LiAlH_4$ reduction of the amide and ester functions, (c) conversion to the enammonium salt, (d) borohydride reduction of the double bond, and (e) CrO_3 oxidation of the alcohol function. With the obtainment of the ketone **22**, the synthesis of the BCD linear tricyclic system was completed by (a) condensation with DMF acetal to yield **23**, (b) reaction with glycine and acetic anhydride to give **24**, and (c) hydrolysis to **25**. In Scheme III, R was methyl, *n*-propyl, allyl, or benzyl. To obtain **25** (R = H), the benzyl group in **24** (R = $CH_2C_6H_5$) was removed by either of two methods. Hydrogenolysis gave **24** (R = H) directly. Alternatively, **24** (R = $CH_2C_6H_5$) on reaction with cyanogen bromide afforded **24** (R = CN), which on reductive cleavage also gave **24** (R = H). On basic hydrolysis, **24** (R = H) led to **25** (R = H). **25** (R = Pr) was synthesized also from **24** (R = H) by alkylation and hydrolysis.

When one examines structures **22–25** and their method of synthesis, *two* formal structural ambiguities are apparent: (1) reduction of **21** to **22** could have given either a cis or trans ring junction in **22**; (2) condensation of DMF acetal with **22** could have taken place on *either* side of the carbonyl group to give **23** or the isomeric **26**. If isomer



26 had been formed, the final pyrrole would have been the angular **27** rather than the desired linear **25**. A priori we expected that a trans ring junction in **22** was favored and that the enamino ketone would be **23** rather than **26** (analogous reductions, steric arguments, etc.). However, conclusive evidence supporting these points was lacking. Two lines of evidence were pursued to remove these ambiguities. First, the ^{13}C NMR spectrum of the maleate salt of **24** (R = $CH_2C_6H_5$) was analyzed. A tabulation of the chemical shifts and peak assignments of the various carbons is given in Table I.

The problem of peak assignments was approached through the use of spectra of model compounds, relative peak intensities, off resonance decoupling, and the general theories relating ^{13}C chemical shift with substitution.[23] The close similarity in the chemical shifts of the α carbons of the pyrrole system implies that the substituents at the two β carbons are very similar. This is supported also by the very close chemical shifts of the two β carbons. Such an inference is in much better accord with linear structure

(17) R. R. Fraser and R. B. Swingle, *Can. J. Chem.*, **48**, 2065 (1970).
(18) J. Saver, A. Mielert, D. Lang, and D. Peter, *Chem. Ber.*, **98**, 1435 (1965).
(19) Method; private communication, B. B. Molloy. Also H. C. Van Der Plas, "Ring Transformation of Heterocycles", Academic Press, London and New York, 1973, p 160.
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(21) J. G. Cannon, G. J. Hatheway, J. P. Long, and F. M. Sharabi, *J. Med. Chem.*, **19**, 987 (1976).
(22) E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, 615 (1949).
(23) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972.

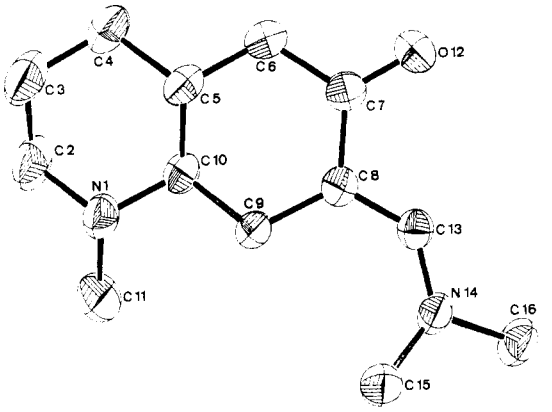


Figure 1. ORTEP stereodrawing of **23** (R = Me). No absolute configuration is implied.

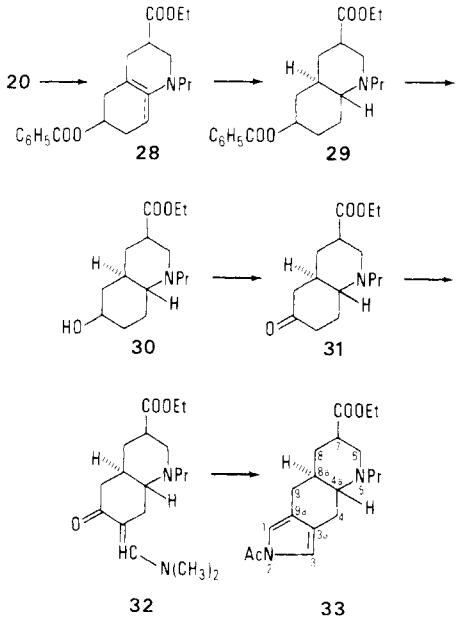
24 than with an angular alternative (**27**). The very similar coupling patterns of the resonances of carbons 3a and 9a suggest that the number of protons two and three bonds removed from these two carbons is very similar. Again, the coupling patterns of carbon-1 and -3 further reinforce this argument. On the question of a cis vs. a trans ring junction, a series of arguments based on the ^{13}C chemical shifts of the sp^3-hybridized carbons led us to conclude that the most probable structure was trans.

Although the NMR arguments were compelling, we undertook an X-ray crystallographic investigation to completely settle the structural questions. The compound chosen for the analysis was the nicely crystalline enamino ketone **23** (R = CH_3), which was the precursor of the pyrrole **25**. The result of this study, which was solved by direct methods, is shown in the ORTEP stereodrawing in Figure 1.

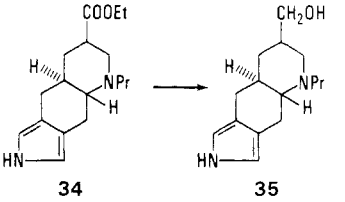
It is evident from the X-ray analysis that the ring junction in the perhydroquinoline **23** is trans and that the condensation of **22** with DMF acetal took place in the least hindered position to give **23**, as shown in Scheme III, and not **26**. The structures of **24** and **25** follow from that of **23**.

With a practical method thus in hand for the synthesis of the "bare" BCD linear tricyclic partial structures **25** ("debenzergolines"), it was of great interest to develop methods also for the synthesis of analogues with substituents corresponding to the carboxyl group in lysergic acid (**2**; Δ^9, R = COOH). This was of importance because it is known[24] that the character of the 8-substituent in an ergoline (**2**) profoundly affects its biological properties. For instance, relatively simple amides of lysergic acid are potent oxytocic drugs,[24] while more complex peptide-like amides are vasoconstrictors.[24] The simple diethyl amide (LSD) is the notorious hallucinogen,[24] and many variously 8-substituted ergolines exhibit dopamine agonist properties.[24] Although decarboxylysergic acid (**2**; Δ^9, R = H), which lacks an 8-substituent, has significant CNS and dopaminergic properties,[25] it is safe to say that an 8-substituent in an ergoline modifies bioactivity in an interesting way. Therefore, with these observations in mind, we developed the synthesis of the tricyclic ester **33** shown in Scheme IV. The route was modeled, in part, after that of Cassady et al.[26]

Scheme IV



Condensation of *p*-(benzoyloxy)cyclohexanone (**20**) with propylamine and ethyl α-(bromomethyl)acrylate gave the octahydroquinoline diester **28**. This was converted to the enammonium salt, which with borohydride was reduced to the *trans*-decahydroquinoline **29**. The diester **29** was hydrolyzed and reesterified to produce the ester–alcohol **30**, which on oxidation with pyridine hydrochloride chromate gave the ketone **31**. Compound **31** on reaction with dimethylformamide dimethyl acetal afforded the eneamino ketone **32**. The ketone **32** on condensation with glycine and then with acetic anhydride, as in Scheme III, gave the desired *N*-acetylpyrrole **33**. Because esters or amides like **33** in the ergoline series show mediocre biological activity, we converted **33** by hydrolysis to the ester **34** and converted **34** by $LiAlH_4$ reduction to the alcohol **35** for evaluation.



Since the ester–amide **33** contains *three* chiral centers, it was of importance to establish its complete stereochemistry. Our own previous work above and Cassady's[26] related studies suggested that the stereochemistry of **33** should be as shown. Nevertheless, we attempted first to confirm the structural assignments by X-ray crystallography. The crystals of **33**, however, proved to be unsuitable for this analysis. More fruitful was a study of the 360-MHz ^1H NMR spectrum of **33**, which confirmed in every detail the stereochemical assignments as shown. Deuteriochloroform solutions proved to be unsuitable for this study; however, deuteriopyridine at 50–60 °C and Me_2SO-d_6 at 70 °C enabled decoupling and assignment of all of the protons. This analysis is summarized in Table II.

The ring-junction protons, 4a and 8a, were used to assign the trans ring junction. H_{8a} appears as a multiplet because of its association with five other protons. However, it occupies trans diaxial relationships with the 8 axial and

(24) A. Hofmann, "Die Mutterkorn Alkaloide", Ferdinand Enke Verlag Stuttgart, 1964. B. Berde and H. O. Schild, "Ergot Alkaloids and Related Compounds", Springer-Verlag, Berlin, Heidelberg, New York, 1978.

(25) N. J. Bach, D. A. Hall, and E. C. Kornfeld, *J. Med. Chem.*, 17, 312 (1974).

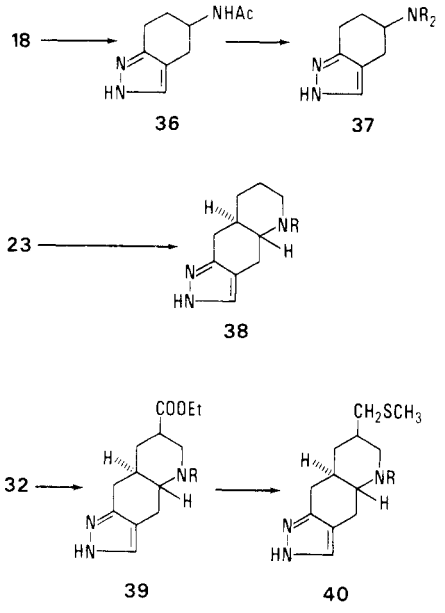
(26) A. M. Crider, J. M. Robinson, H. G. Floss, J. M. Cassady, and J. A. Clemens, *J. Med. Chem.*, **20** (11), 1473 (1977).

Table II. 360-MHz ^{1}H NMR Peak Assignments (ppm) of Tricyclic Ester 33[a]

	Pyd_5, 50-60 °C	Me_2SO-d_6, 70 °C
4_{ax}	2.57	2.45
4_{eq}	3.16	3.25
4a	2.44	3.00
6_{ax}	2.65	2.95
6_{eq}	3.54	3.57
7	3.00	2.84
8_{ax}	1.37	1.41
8_{eq}	2.18	2.14
8a	1.84	1.85
9_{ax}	2.21	2.44
9_{eq}	2.68	2.78
CH_2	1.55	1.63
CH_2	~2.67/2.94	~3.15/3.00
CH_3	0.85	0.91
$COOCH_2$	4.16	4.12
CH_3	1.17	1.18

[a] ax = axial; eq = equatorial.

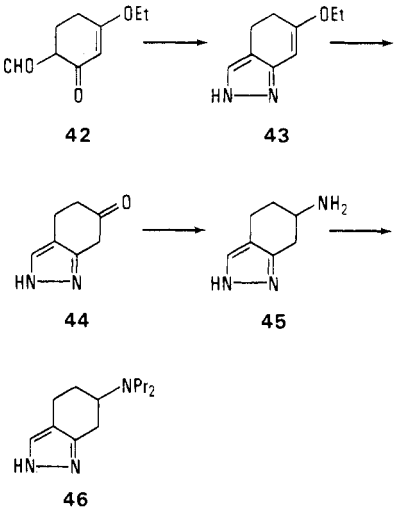
Scheme V



9 axial protons. H_{4a} appears as a doublet of doublets of doublets (ddd), of which two of the couplings are large (~11 Hz) and one medium (~6 Hz). This pattern can arise only from two diaxial and one axial/equatorial orientation. In addition, it has been shown that H_7 is axial. The spectra also show long-range coupling from H_6 equatorial to H_8 equatorial. This results from a "W" relationship of these two protons. The information collectively places the piperidine ring in the normal chair conformation.

BC Bicyclic and BCD Tricyclic Pyrazole Ergoline Analogues. With good methods in hand for the synthesis of enamino ketones **18** (Scheme II), **23** (Scheme III), and **32** (Scheme IV), it was of interest to explore the conversion of these intermediates to bicyclic and tricyclic pyrazole analogues of the ergolines. This interest was based on the fact that pyrazoles are isosteric with pyrroles and also on the known greater stability to acid and oxidants of pyrazoles vs. pyrroles. We were also aware that certain nonrigid pyrazoleethylamines have been reported to have dopaminergic activity.[27] It was hoped, therefore, that the pyrazole analogues of the pyrroles **11**, **25**, and **35** would have dopamine agonist properties and at the same time would have improved metabolic stability.

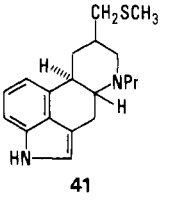
Scheme VI



Consequently, the three enamino ketones **18**, **23**, and **32** (Scheme V) were converted simply on reaction with hydrazine into the pyrazoles **36**, **38**, and **39** (and/or the alternate tautomers thereof). Conversion of the amide **36** to the amines **37** (R = H, Me, Pr) was accomplished by hydrolysis and reductive amination.

Compound **38** (R = Pr) was made via the *N*-cyano compound **23** (R = CN), which gave **38** (R = CN) with hydrazine. **38** (R = CN) was cleaved in the usual way to **38** (R = H), and this on reductive amination afforded **38** (R = Pr).

Since ester **39** was not expected to show high biological activity, because of hydrolysis in vivo, it was converted to the sulfide **40** for evaluation. This derivative was chosen because it is known[28] that the methylthiomethyl side chain, as present in the ergoline drug pergolide [8β-[(methylthio)methyl]-6-propylergoline; **41**], contributes to the potent dopaminergic properties of the molecule.



Ester **39** (R = Pr) was reduced by $LiAlH_4$ to the corresponding carbinol. The carbinol was then converted to the mesylate ester, which with CH_3SNa afforded the thioether **40**.

For purposes of comparison with the pyrazoles in Scheme V, a bicyclic pyrazole **46**, isomeric with **37**, was synthesized as outlined in Scheme VI. The keto aldehyde **42**[29] was condensed with hydrazine to yield the enol ether **43**. Acid hydrolysis of **43** gave the ketone **44**, which on reductive amination afforded the amines **45** and **46**.

It should be noted in concluding this description of the chemistry that all of the end products in Schemes I through VI are *racemic*. Studies on the resolution of **6**, **11**, **25**, **38**, **40**, etc. are in progress. It is our expectation that enantiomers of the partial structures with an absolute

(27) K. Fuxe, L. F. Agnati, and U. Ungerstedt, *Eur. J. Pharmacol.*, **35**, 93 (1976); C. A. Seyfried and K. Fuxe, *Arch. Pharmacol.*, **302** (Suppl. R60), 237 (1978).

(28) R. W. Fuller, J. A. Clemens, E. C. Kornfeld, H. D. Snoddy, E. B. Smalstig, and N. J. Bach, *Life Sci.*, **24**, 375 (1979).

(29) E. Wenkert, L. H. Lau, and W. D. Fellows, *J. Org. Chem.*, **27**, 2278 (1962).

Table III. Dopaminergic Activity of Ergoline Analogues

			prolactin inhibition[a]					rat turning[b]		
no.	R	salt	dose mg/kg, ip	prolactin control, ng/mL	prolactin treatment, ng/mL	inhibn, %	signif level (p)	dose, mg/kg ip	% of rats exhibiting turning	av turns/ 1st 15 min[c]
6	Me	oxalate	5.0	36.4 ± 3.2	3.2 ± 0.5	91	<0.001	1.0	75	69
			0.05	36.4 ± 3.2	19.9 ± 3.6	45	<0.01	0.1	0	0
6	Pr	oxalate	5.0	55.2 ± 4.1	3.0 ± 0.3	95	<0.001			
			0.5	46.1 ± 3.6	18.9 ± 4.4	59	<0.001	1.0	60	113
			0.05	46.1 ± 3.6	46.2 ± 4.7	0	<0.9 NS	0.1	40	73
11	H		5.0	49.8 ± 6.7	38.0 ± 3.5	24	<0.2 NS	1.0	0	0
11	Et	maleate	5.0	49.8 ± 6.7	38.2 ± 2.7	23	<0.2 NS	1.0	0	0
11	Pr	maleate	5.0	59.8 ± 6.3	4.0 ± 0.2	93	<0.001			
			0.5	59.8 ± 6.3	36.1 ± 3.0	40	<0.01	1.0	40	52
			0.05	59.8 ± 6.3	47.6 ± 5.5	20	<0.2 NS	0.1	0	0
25	H	maleate	5.0	43.4 ± 6.1	31.9 ± 7.8	26	<0.3 NS	1.0	0	0
25	Me	maleate	5.0	36.4 ± 3.2	3.8 ± 0.5	90	<0.001			
			0.5	37.7 ± 4.0	30.9 ± 6.3	18	<0.4 NS	1.0	33	19
25	Pr	maleate	5.0	43.4 ± 6.1	2.0 ± 0.1	95	<0.001	1.0	100	169
			0.05	49.5 ± 3.9	31.6 ± 3.1	36	<0.01	0.1	50	64
			0.005	49.5 ± 3.9	37.6 ± 4.2	24	<0.1 NS	0.05	33	49
35			0.05	35.6 ± 3.7	29.5 ± 12.4	17	<0.3 NS	1.0	100	109
								0.1	67	8
37	H	2HCl	5.0	49.8 ± 6.7	42.7 ± 2.8	14	<0.4 NS	1.0	0	0
37	Me	2HCl	5.0	59.8 ± 6.3	18.5 ± 1.9	69	<0.001			
			0.05	59.8 ± 6.3	41.0 ± 4.5	32	<0.05	1.0	0	0
37	Pr	2HCl	5.0	37.6 ± 6.3	2.3 ± 0.1	94	<0.001			
			0.5	31.2 ± 2.6	10.6 ± 2.0	66	<0.001	1.0	60	90
			0.05	31.2 ± 2.6	30.8 ± 5.0	1	<0.2 NS	0.1	0	0
38	H	2HCl	5.0	31.7 ± 2.6	25.4 ± 4.5	20	<0.3 NS	1.0	0	0
38	Me	2HCl	5.0	31.7 ± 2.6	5.0 ± 0.5	84	<0.001			
			0.5	31.7 ± 2.6	18.5 ± 1.3	42	<0.001	1.0	0	0
			0.05	31.7 ± 2.6	31.1 ± 3.2	2	<0.9 NS			
38	Pr	2HCl	5.0	31.7 ± 2.6	2.7 ± 0.3	91	<0.001	1.0	100	85
			0.5	31.7 ± 2.6	7.7 ± 4.0	76	<0.001	0.1	75	67
			0.05	31.7 ± 2.6	12.3 ± 1.3	61	<0.001	0.05	67	6
38	allyl	2HCl	0.05	17.9 ± 2.5	12.4 ± 1.8	31	<0.1 NS	1.0	100	165
								0.1	0	0
40	Pr	2HCl	0.05	44.9 ± 6.4	4.8 ± 0.5	89	<0.001	1.0	100	81
			0.005	44.9 ± 6.4	19.3 ± 1.3	57	<0.001	0.1	50	65
			0.0005	44.9 ± 6.4	31.5 ± 4.0	30	<0.1 NS	0.05	67	80
41		MesOH	0.05	30.4 ± 3.4	1.6 ± 0.4	95	<0.001	1.0	100	93
								0.1	83	81
			0.005	37.7 ± 4.0	3.5 ± 0.6	91	<0.001	0.05	100	60
			0.0005	37.7 ± 4.0	15.5 ± 2.2	59	<0.001	0.02	0	0
46	Pr		0.05	27.7 ± 1.9	19.0 ± 2.2	31	<0.01	1.0	100	114
								0.1	0	0

[a] Values are means plus or minus standard error for 10 rats. [b] Values are based on 6–10 rats per group. [c] After turning began.

configuration related to that of the ergolines (**2**) should have enhanced activity over the racemates.

Pharmacology. The dopaminergic properties of the new ergoline analogues were evaluated using two standard methods, and the results are listed with those of the reference drug pergolide (**41**) in Table III. In the first method, the lowering of serum prolactin levels by the drugs in reserpinized male rats was measured according to a method of Clemens et al.[26] Secondly, the contralateral rotational behavior of unilateral 6-hydroxydopamine nigrostriatal-lesioned rats was measured using the method of Ungerstedt and Arbuthnot.[30]

The following conclusions may be made based on the results as summarized in Table III: (a) *All* of the classes show significant dopaminergic activity. (b) The primary and secondary amines are weakly active when compared to the tertiary amines. (c) The propyl compounds are usually more potent than the ethyl and methyl homologues. (d) The *tricyclic* partial structures, both ABC and BCD, are more active than the *bicyclic* compounds. (e) The pyrazoles interestingly appear to be no less potent

(30) U. Ungerstedt and G. W. Arbuthnott, *Brain Res.*, **24**, 485 (1970).

than the related pyrroles. (f) The most active compounds are the linear BCD tricyclic pyrazoles **38** (R = Pr) and **40** (R = Pr), which are quite similar in potency to the highly active ergoline pergolide (**41**). (g) Some lack of parallelism in prolactin inhibition vs. rat turning is noted. For example **6** (R = Me) and **25** (R = Pr) are about equipotent in prolactin inhibition at 0.05 mg/kg. However, there is a wide difference in turning (0 vs. 50%). These observations may be explained by differences in transport efficiency of the drugs to the pituitary and to the brain, respectively.

The results reported here give strong support to the hypothesis that the pyrroleethylamine moiety of the ergolines is, in fact, the dopamine agonist active portion of the class. It is evident also that the benzene ring of an ergoline is *not* essential for dopaminergic activity.

Of further interest is the observation that the new partial structures appear to be "cleaner" or "purer" dopaminergic agents than the ergolines. For instance, isolated smooth muscle testing of the linear BCD compounds shows none of the serotonin antagonist (or agonist) or α-blocking activities seen with many of the ergolines. Additional studies on the biological evaluation of the series will be published elsewhere.

Experimental Section

Elemental analyses are indicated only by symbols of the elements and are within 0.4% of the theoretical values. All new compounds were monitored by measurement of IR, UV, and NMR spectra. Mass spectra were determined also for most structures and were consistent with other spectral measurements. Melting points were determined on a Mel-Temp apparatus and are corrected. All reactions were followed by TLC carried out on Merck F254 silica gel plates. ^{1}H NMR, 360 MHz, spectra were measured on a Bruker WH-360 spectrometer; ^{13}C NMR spectra were measured on a JEOL PFT-100 spectrometer.

3-(2-Aminoethyl)pyrrole (5) Maleate Salt. The method of Osanova and Piskov[12] was used, except that the product was isolated as the maleate salt, mp 86–88 °C, from EtOH–ether. Anal. ($C_{10}H_{14}N_2O_4$) C, H, N, O.

1-Benzoyl-4-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (8).[16] To 20.0 g (0.072 mol) of 1-benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole[15] in 500 mL of benzene was added 7.7 g (0.024 mol) of ZnI_2. The solution was stirred and heated under reflux under N_2 for 1.5 h. It was cooled, diluted with EtOAc, washed with H_2O, and dried over Na_2SO_4. The solvent was distilled, and the product was crystallized from Et_2O–benzene: yield 16.9 g (84%); mp 146–149 °C.

4-Amino-1-benzoyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (9). To a mixture of 2.77 g (10 mmol) of the β-tetralone **8** and 7.7 g (100 mmol) of NH_4OAc in 125 mL of MeOH was added 590 mg (10 mmol) of $NaCNBH_3$. The solution was stirred at 25 °C for 22 h, after which it was poured into ice and excess 1 N HCl. The mixture was washed with $CHCl_3$, and the acid layer was made basic with NH_4OH. The product was extracted with several portions of $CHCl_3$. The extracts were washed with aqueous NaCl, dried (Na_2SO_4), and evaporated. The product was crystallized from CH_2Cl_2–Et_2O: mp 118–120 °C; yield 1.78 g (64%). Anal. ($C_{18}H_{18}N_2O$) C, H, N.

4-(Dimethylamino)-1,3,4,5-tetrahydrobenz[*cd*]indole[13] (6; R = Me) Oxalate Salt. A solution of 4.5 g (16.2 mmol) of the primary amine **9** in 100 mL of MeOH was treated with 1.0 g (16.2 mmol) of $NaCNBH_3$ and 7.5 mL of 37% aqueous formaldehyde. The mixture was stirred at 25 °C under N_2 for 66 h. It was then poured into ice and excess 1 N HCl. The resulting solution was washed with Et_2O, made basic with NH_4OH, and extracted with $CHCl_3$–*i*-PrOH. The extracts were washed with saturated NaCl, dried (Na_2SO_4), and evaporated. The crude, residual tertiary amine **10** (R = Me; 4.8 g) was hydrolyzed by refluxing a solution containing it in 100 mL of 6 N HCl under N_2 for 45 min. The solution was poured onto ice and made basic with NH_4OH, and the product was extracted with $CHCl_3$–*i*-PrOH. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The residual indoline was dissolved in 200 mL of $CHCl_3$, and 25 g of MnO_2 was added. The suspension was stirred at 25 °C for 2 h. The solid was filtered, washed with $CHCl_3$, and discarded. The combined filtrates were concentrated, and the crude product was purified by chromatography on 150 g of Florisil using $CHCl_3$/2–10% MeOH as eluant: yield 0.71 g (22%). The oxalate salt was prepared in EtOH: yield 305 mg; mp 235–237 °C dec. Anal. ($C_{28}H_{34}N_4O_4$) C, H, N.

4-(Dipropylamino)-1,3,4,5-tetrahydrobenz[*cd*]indole (6; R = Pr) Oxalate Salt. This was prepared from 3.9 g (14 mmol) of the primary amine **9** using 6.6 mL (90 mmol) of propionaldehyde and 900 mg (14 mmol) of $NaCNBH_3$ in the reductive amination. The product **10** (R = Pr; 5 g) was hydrolyzed using 120 mL of 6 N HCl, and the indoline (3.6 g) was aromatized using 20 g of MnO_2 as above. The indole (1.5 g) was converted to the oxalate salt: yield 1.07 g (22%); mp 194–196 °C dec. Anal. ($C_{19}H_{26}N_2O_4$) C, H, N.

4-Acetamido-1-ethoxycyclohexene (13). A solution of 6.7 g of *p*-acetamidocyclohexanone (**12**)[17] in 150 mL of absolute EtOH and 25 mL of ethyl orthoformate containing a few crystals of *p*-toluenesulfonic acid hydrate was stirred at 25 °C for 16 h. The mixture was concentrated in vacuo, and the residue was dissolved in 200 mL of toluene. The solution was distilled slowly at atmospheric pressure under N_2 until there was no more diethyl ketal evident by TLC. The solution was cooled, washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated. The residual product was crystallized from Et_2O–hexane: mp 100–102 °C; yield 6.2 g (78%). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 64.90; H, 8.69; N, 7.22.

6-Acetamido-1,4-bis(methoxycarbonyl)phthalazine (15). A solution of 765 mg (4.2 mmol) of the enol ether **13** in 10 mL of dioxane was added rapidly to a solution of 910 mg (4.6 mmol) of the tetrazine dicarboxylic ester[18] **14** in 25 mL of dioxane. The mixture was stirred at 25 °C for 72 h and then evaporated in vacuo. The crude product was purified by chromatography on 30 g of Florisil using $CHCl_3$/2–5% MeOH as eluant. The product was crystallized from MeOH–Et_2O: mp 143–144 °C; yield 940 mg (73%). Anal. ($C_{14}H_{17}N_3O_5$) C, H, N.

5-Acetamido-1,3-bis(methoxycarbonyl)-4,5,6,7-tetrahydroisoindole (16). A mixture of 2.59 g of the phthalazine diester **15** and 5 g of zinc dust in 100 mL of HOAc was stirred for 6 h. Additional zinc dust (5 g) was added and stirring was continued for a total of 22 h. The suspension was filtered, and the filtrate was poured onto ice and made basic with NH_4OH. The product was extracted with $CHCl_3$–*i*-PrOH, and the extract was washed with brine, dried, and concentrated. The pyrrole diester **16** was crystallized from ether: mp 228–230 °C; yield 1.83 g (73%). Anal. ($C_{14}H_{18}N_2O_5$) C, H, N.

5-Acetamido-4,5,6,7-tetrahydroisoindole-1,3-dicarboxylic Acid. A solution of the diester **16** (1.83 g, 6.2 mmol) in 150 mL of THF and 25 mL of 2 N NaOH was heated under reflux under N_2 for 5 h. It was concentrated in vacuo, and the residue was taken up in H_2O. The aqueous solution was filtered and acidified with 1 N HCl. The product was filtered and crystallized from benzene–MeOH: mp 233–235 °C; yield 890 mg (54%). Anal. ($C_{12}H_{14}N_2O_5$) C, H, N.

***N*-[3-[(Dimethylamino)methylene]-4-oxocyclohexyl]-acetamide (18).** A solution of 15.5 g (0.1 mol) of 4-acetamidocyclohexanone (**12**),[17] 80 g of DMF dimethyl acetal, and 1.5 mL of triethylamine in 500 mL of benzene was distilled over a period of 1.5 h to about one-half the original volume. Benzene (250 mL) was then added to the residue, and heating was continued just below the boiling point for 2 h. Distillation was continued to a volume one-half of the original during 1.75 h. Benzene (250 mL) was again added, and the process was repeated a third time. The solution was cooled, and the product was filtered: yield 6.45 g; mp 128–131 °C. The filtrate material was chromatographed on 200 g of Florisil using $CHCl_3$/0–5% MeOH as eluant. Starting material (2.45 g, 16%) and additional product (5.55 g) were obtained: total yield 57%. Anal. ($C_{11}H_{18}N_2O_2$) C, H, N.

5-Acetamido-2-acetyl-4,5,6,7-tetrahydroisoindole (19). To a solution of glycine, 9.0 g (0.12 mol), and KOH, 6.7 g (0.12 mol), in 400 mL of absolute EtOH was added 22.6 g (0.108 mol) of the enamino ketone **18**. The resulting mixture was heated under reflux under N_2 for 1.75 h, after which it was diluted with ether. The potassium salt was filtered and added to 400 mL of Ac_2O. The solution was then refluxed under N_2 for 1 h. Excess Ac_2O was distilled in vacuo, and the residue was taken up in $CHCl_3$. In-

soluble material was filtered, and the filtrate was chromatographed on 350 g of Florisil using $CHCl_3$/0–2% MeOH as eluant. The product, which was in some of the later fractions, was crystallized from ether: mp 148–150 °C; yield 10.3 g (45%). Anal. ($C_{12}H_{16}N_2O_2$) C, H, N.

5-Amino-4,5,6,7-tetrahydroisoindole (17). A. Decarboxylation of the Diacid Obtained from 16. The amide diacid above, derived from the amide diester **16**, 850 mg (3.2 mmol), was heated in 25 mL of quinoline with 50 mg of copper powder, under N_2, up to 200 °C. Heating at 200–210 °C was continued for 15 min. The mixture was poured onto ice and extracted with $CHCl_3$, and the extract was washed with dilute HCl, 10% NaOH, and H_2O and dried (Na_2SO_4). The solvent was distilled, and the crude product, 260 mg (46%), was purified by chromatography on Florisil. The product was identified as 5-acetamido-4,5,6,7-tetrahydroisoindole by comparison of TLC, NMR, IR, and MS with those of the same monoamide obtained in the following experiment.

B. Hydrolysis of Diamide 19. A mixture of 590 mg (2.7 mmol) of the diamide **19**, 50 mL of dioxane, and 25 mL of 20% KOH was heated under reflux for 17.5 h. The solution was diluted with H_2O and extracted with $CHCl_3$, and the extract was washed with brine, dried (Na_2SO_4), and concentrated. These conditions gave the same 5-acetamido-4,5,6,7-tetrahydroisoindole as obtained in A above (TLC, NMR, IR, MS). Complete hydrolysis to **17** was accomplished as follows: A solution of the diamide **19**, 5.1 g (0.0232 mol), 50 g of NaOH, 50 mL of H_2O, and 200 mL of EtOH was refluxed under N_2 for 16 h. Water was added, and the mixture was extracted with CH_2Cl_2. The extract was washed with saturated NaCl and dried (Na_2SO_4), and the solvent was distilled. A $CHCl_3$ solution of the crude product was filtered through 105 g of Al_2O_3 (II), and the solvent was distilled: yield 2.52 g (80%); mp ~130 °C. A suitable solvent for recrystallization of the unstable base was not found, and crystalline salts were not obtained. Therefore, compound **17** was characterized as the following tertiary amine derivatives **11**.

5-(Diethylamino)-4,5,6,7-tetrahydroisoindole (11; R = Et) Maleate Salt. A solution of 2.52 g (18.5 mmol) of the primary amine (**17**), 1.2 g (18.5 mmol) of $NaCNBH_3$, and 6 mL (110 mmol) of acetaldehyde in 100 mL of MeOH was stirred at 25 °C under N_2 for 16.5 h. The mixture was diluted with aqueous $NaHCO_3$ and extracted with $CHCl_3$, and the extracts were washed with brine, dried (Na_2SO_4), and evaporated. The rather unstable pyrrole derivative was purified by chromatography twice on 35 g of Florisil using $CHCl_3$/2–4% MeOH in the elution. The purified base (**11**; R = Et), 0.66 g (19%), was converted to the maleate salt in MeOH–Et_2O: mp 81–83 °C; yield 385 mg. Anal. ($C_{16}H_{24}N_2O_4$) C, H, N.

5-(Dipropylamino)-4,5,6,7-tetrahydroisoindole (11; R = Pr) Maleate Salt. The reductive amination of the primary amine (**17**) was conducted in this case with propionaldehyde. The pure base (**11**; R = Pr) after chromatography was converted to the maleate salt in MeOH–Et_2O: mp 134–137 °C dec; yield 38%. Anal. ($C_{18}H_{28}N_2O_4$) C, H, N.

6-(Benzoyloxy)-3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinone (21; R = H). A solution of 52 g (0.24 mol) of 4-(benzoyloxy)-cyclohexanone (**20**),[22] 30 mL of pyrrolidine, and a few crystals of *p*-toluenesulfonic acid hydrate in 1000 mL of benzene was refluxed under a Dean–Stark water separator for 1 h. The benzene was distilled in vacuo, and the residue was dissolved in 1000 mL of dioxane. Acrylamide, 42.6 g (0.6 mol), was added, and the solution was heated under reflux under N_2 for 21 h. The solvent was distilled under reduced pressure, and the crude product was chromatographed twice on Florisil using $CHCl_3$/0–2% MeOH: yield 46.5 g (72%); mp 115–132 °C. NMR analysis indicated that the product was a mixture of double-bond isomers containing about equal amounts of the $\Delta^{4a,8a}$ and $\Delta^{8,8a}$ isomers. Anal. ($C_{16}H_{17}NO_3$) C, H, N.

***trans*-7-[(Dimethylamino)methylene]octahydro-1-(phenylmethyl)-6(2*H*)-quinolinone (23; R = $CH_2C_6H_5$).** In the following procedure, several intermediates were noncrystalline, but each was homogeneous by TLC and was characterized by appropriate physical methods (NMR, IR, UV, MS). The lactam ester **21** (R = H; 56 g, 0.21 mol) was dissolved in a mixture of 250 mL of THF and 250 mL of DMF. Sodium hydride (50% in mineral oil), 11.0 g (0.23 mol), was added, and the mixture was stirred for 30 min. A solution of benzyl bromide, 39.3 g (0.23 mol), in 60 mL of THF was then added dropwise, during which the temperature rose to 55 °C. The mixture was stirred for 1 h after the addition was complete. EtOAc was added, and the solution was washed well with H_2O and brine and dried (Na_2SO_4). Removal of the solvent left 83 g of the crude 6-(benzoyloxy)-3,4,5,6,7,8-hexahydro-1-(phenylmethyl)-2(1*H*)-quinolinone. The product was dissolved in 750 mL of THF, and 30 g of $LiAlH_4$ was added in portions with stirring and cooling. The reduction was completed by heating the reaction mixture under reflux for 4.75 h. The solution was then treated cautiously with EtOAc, 10% NaOH, and H_2O. $CHCl_3$ was used to extract the product, and the extract was washed with brine, dried (Na_2SO_4), and evaporated. The crude 1-benzyl-6-hydroxy-1,2,3,4,5,6,7,8-octahydroquinoline was dissolved in 500 mL of Et_2O, and dry HCl was used to prepare the $\Delta^{1,8a}$-enammonion salt. The salt was filtered and then dissolved in a mixture of 400 mL of THF and 100 mL of MeOH. $NaCNBH_4$, 20 g, was then added with stirring and cooling in ice. The cooling bath was removed, and stirring was continued for 1.5 h. The reaction mixture was poured onto ice and 1 N HCl, and the resulting mixture was washed with Et_2O. The aqueous layer was made basic with NH_4OH, and the product was extracted with $CHCl_3$. The extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). Evaporation of the solvent left 47 g (0.19 mol, 93%) of crude 1-benzyl-6-hydroxy-*trans*-decahydroquinoline. The secondary alcohol was dissolved in 700 mL of 6 N H_2SO_4, and the solution was cooled in ice. A solution of 19 g (0.19 mol) of CrO_3 in 100 mL of 6 N H_2SO_4 was added dropwise with continued cooling, after which stirring was continued at 25 °C for 2 h. The mixture was poured onto ice, made basic with Na_2CO_3 and NH_4OH, and extracted with $CHCl_3$. The extracts were washed with saturated NaCl, dried (Na_2SO_4), and evaporated. The crude product was purified by chromatography on Florisil; the yield of *trans*-octahydro-1-(phenylmethyl)-6(2*H*)-quinolinone (**22**; R = $CH_2C_6H_5$) was 4.8 g (10%). The ketone was then mixed with 100 g of DMF dimethyl acetal, and the solution was heated under reflux for 70 h. The mixture was concentrated under reduced pressure, and the product was purified by chromatography on Florisil using $CHCl_3$/0–4% MeOH as eluant: yield 3.2 g (54%). A sample was crystallized from Et_2O–hexane, mp 109–111 °C. Anal. ($C_{19}H_{26}N_2O$) C, H, N.

***trans*-(±)-7-Acetyl-2,3,4,4a,5,7,9,9a-octahydro-1-(phenylmethyl)-1*H*-pyrrolo[3,4-*g*]quinoline (24; R = $CH_2C_6H_5$) Maleate Salt.** Glycine, 1.3 g (17 mmol), and 950 mg (17 mmol) of KOH were dissolved in 150 mL of EtOH. The enamino ketone **23** (R = $CH_2C_6H_5$), 4.7 g (15.8 mmol), was added, and the resulting solution was heated under reflux for 4 h. The mixture was concentrated in vacuo. Ether was added, and the solid product was filtered and added to 200 mL of Ac_2O. The suspension was heated under reflux under N_2 for 45 min and concentrated in vacuo, and the residue was diluted with H_2O and made basic with $NaHCO_3$. The product was extracted with $CHCl_3$, and the extract was washed with H_2O and brine and dried (Na_2SO_4). Distillation of the solvent left the crude product, which was purified by chromatography on 150 g of Florisil using $CHCl_3$–2% MeOH in the elution: yield 3.7 g (76%). The maleate salt was prepared from a portion of the base and crystallized from MeOH–Et_2O, mp 162–164 °C. Anal. ($C_{24}H_{28}N_2O_5$) C, H, N.

***trans*-(±)-7-Acetyl-2,3,4,4a,5,7,9,9a-octahydro-1*H*-pyrrolo[3,4-*g*]quinoline (24; R = H) Maleate Salt.** The crude *N*-benzylpyrrolamide **24** (R = $CH_2C_6H_5$), 3.5 g (0.0114 mol), in 196 mL of EtOH was hydrogenolyzed at 4 atm of hydrogen pressure during 2 h using 0.5 g of 5% Pd/C. TLC indicated that the reaction was incomplete. Nevertheless, the catalyst was filtered, and the solvent was distilled. A solid was filtered, 0.5 g (20%), and this was purified by conversion to the maleate salt in MeOH–ether: yield 340 mg; mp 150–151 °C. Anal. ($C_{17}H_{22}N_2O_5$) C, H, N.

***trans*-(±)-7-Acetyl-2,3,4,4a,5,6,9,9a-octahydro-1-cyano-1*H*-pyrrolo[3,4-*g*]quinoline (24; R = CN).** Chromatographically purified *N*-benzyl compound **24** (R = $CH_2C_6H_5$) was obtained from 3.2 g (0.0107 mol) of the enamino ketone **23** (R = $CH_2C_6H_5$) as described above. This was dissolved in 200 mL of CH_2Cl_2, and 4 g (0.038 mol) of CNBr was added. The solution was stirred at 25 °C under N_2 for 16 h. The solvent was evaporated under reduced pressure, and the crude residual product was purified

by chromatography on 200 g of Florisil: mp 135–137 °C from Et_2O; yield 630 mg (27%). Anal. ($C_{14}H_{17}N_3O$) C, H, N.

***trans*-(±)-2,3,4,4a,5,7,9,9a-Octahydro-1*H*-pyrrolo[3,4-*g*]quinoline (25; R = H) Maleate Salt.** A mixture of 0.4 g (1.75 mmol) of the *N*-cyano amide **24** (R = CN), 50 mL of HOAc, 10 mL of H_2O, and 2 g of zinc dust was stirred and refluxed under N_2 for 19 h. Solids were filtered, and the filtrate was poured onto ice, made basic with NH_4OH, and extracted with $CHCl_3$–*i*-PrOH. The extracts were washed with saturated NaCl, dried (Na_2SO_4), and evaporated. The residual pyrrolamide **24** (R = H) was hydrolyzed by stirring for 0.75 h in a mixture of 15 mL of MeOH and 2 mL of 2 N NaOH. The solution was diluted with H_2O and extracted with $CHCl_3$–*i*-PrOH. The extracts were washed with brine, dried (Na_2SO_4), and evaporated. The maleate salt was prepared in and crystallized from MeOH–Et_2O: yield 200 mg (39%); mp 190 °C. Anal. ($C_{15}H_{20}N_2O_4$) C, H, N.

***trans*-(±)-2,3,4,4a,5,6,9,9a-Octahydro-1-propyl-1*H*-pyrrolo[3,4-*g*]quinoline (25; R = Pr) Maleate Salt.** The *N*-cyano amide **24** (R = CN), 0.6 g (2.6 mmol), was mixed with 50 mL of HOAc, 10 mL of H_2O, and 3 g of zinc dust. The mixture was stirred and refluxed under N_2 for 6.25 h. Solids were filtered, and the filtrate was poured onto ice, made basic with NH_4OH, and extracted thoroughly with $CHCl_3$–*i*-PrOH. The extracts were washed with brine, dried (Na_2SO_4), and evaporated. To the residual secondary amine **24** (R = H) was added 50 mL of DMF, 0.8 g of K_2CO_3, and 0.4 mL of *n*-propyl iodide. The mixture was stirred under N_2 at 25 °C for 16 h and diluted with H_2O, and the product was extracted with EtOAc. The extract was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The crude pyrrolamide **24** (R = Pr) was hydrolyzed by stirring under N_2 for 65 min a solution of it in 20 mL of MeOH and 3 mL of 2 N NaOH. The solution was diluted with H_2O and extracted well with $CHCl_3$, and the extracts were washed with brine, dried (Na_2SO_4), and evaporated. The maleate salt of the product was prepared in MeOH–Et_2O: yield 215 mg (25%); mp 168–170 °C dec. Anal. ($C_{18}H_{26}N_2O_4$) C, H, N.

6-(Benzoyloxy)-3,4,5,6,7,8-hexahydro-1-methyl-2(1*H*)-quinolinone (21; R = Me). To a solution of 2.71 g (10 mmol) of the lactam ester **24** (R = H) in 200 mL of THF and 5 mL (80 mmol) of CH_3I was added 580 mg of NaH (50% in mineral oil, 12 mmol). The mixture was stirred under N_2 for 15.5 h and was then diluted with H_2O and extracted with $CHCl_3$–*i*-PrOH. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The product was purified by chromatography on 30 g of Florisil. $CHCl_3$/0–1% MeOH was used in the elution. The crude product, 2.62 g (75%), was crystallized from Et_2O–hexane: mp 100–102 °C; yield 1.4 g (49%). Anal. ($C_{17}H_{19}NO_3$) C, H, N. NMR analysis indicated that the product was a mixture of $\Delta^{4a,8a}$ and $\Delta^{8,8a}$ double-bond isomers. Other runs conducted in dimethoxyethane of reflux resulted in loss of the benzoate group to give 6-hydroxy-3,4,5,6,7,8-hexahydro-1-methyl-2(1*H*)-quinolinone, mp 112–117 °C from Et_2O–hexane. Anal. ($C_{10}H_{16}NO_2$) C, H, N.

***trans*-7-[(Dimethylamino)methylene]octahydro-1-methyl-6(2*H*)-quinolinone (23; R = Me).** In this experiment, the various intermediates were noncrystalline; however, each was homogeneous by TLC and was characterized by appropriate physical measurements (IR, NMR, MS, etc.). The crude lactam benzoate ester **21** (R = Me), 47.3 g (0.166 mol), was dissolved in 800 mL of THF. $LiAlH_4$ (20 g) was then added in portions while stirring and cooling in ice. The mixture was then heated under reflux for 4 h, cooled, and treated carefully with EtOAc and 10% NaOH. Water was added, and the product was extracted with $CHCl_3$–*i*-PrOH. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in Et_2O, and dry HCl was used to convert the product to the $\Delta^{1,8a}$-enammonium chloride salt. The Et_2O was decanted, and the crude salt was dissolved in a mixture of 50 mL of MeOH and 200 mL of THF. $NaCNBH_3$, 12 g (0.2 mol), was then added in portions with stirring while cooling the mixture in ice. The cooling bath was removed, and stirring was continued for 1 h. The reaction mixture was poured onto ice and 1 N HCl. It was washed with $CHCl_3$, and the aqueous layer was made basic with NH_4OH. The product was extracted thoroughly with $CHCl_3$–*i*-PrOH, and the extract was washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The residual 6-hydroxy-1-methyl-*trans*-decahydroquinoline was obtained as an oil: yield 15 g (54%) (0.089 mol). It was dissolved in 250 mL of 6 N H_2SO_4, and the solution was cooled in ice. To it was then added dropwise with stirring in 10 min a solution of 9.0 g (0.09 mol) of CrO_3 in 60 mL of 6 N H_2SO_4. The mixture was stirred an additional hour at 25 °C. Excess oxidant was decomposed with *i*-PrOH, and the solution was poured onto ice, made basic with NH_4OH, and extracted well with $CHCl_3$–*i*-PrOH. The extracts were washed with saturated NaCl, dried (Na_2SO_4), and concentrated. The residual *trans*-octahydro-1-methyl-6(2*H*)-quinolinone (**22**; R = Me) was distilled under reduced pressure: bp 105–116 °C (6 mm); yield 6.7 g (45%). A solution of the ketone **22** (R = Me) in 100 g of DMF dimethyl acetal was heated under reflux for 20 h. The mixture was concentrated in vacuo, and the residue was chromatographed on 150 g of Florisil using CH_2Cl_2/1–5% MeOH in the elution. The enamino ketone **23** (R = Me) was obtained as a solid in one of the later chromatographic fractions: yield 3.0 g (34%). It was crystallized from ether: yield 590 mg; mp 107–109 °C. Anal. ($C_{13}H_{22}N_2O$) C, H, N.

X-Ray Structure Determination. Compound **23** (R = Me) crystallized from ether as colorless needles in the centrosymmetric monoclinic space group, $P21/n$, with four molecules in a unit cell having the dimensions: a = 18.506, 0.002 Å; b = 5.810, 0.001 Å; c = 12.047, 0.002 Å; β = 92.600, 0.02 Å.

The density calculated for $C_{13}H_{22}N_2O$ (M_r 222.3) is 1.14 g cm^{-3}, and the density observed by flotation is 1.13 g cm^{-3}. The intensities of 1989 reflections, of which 387 were considered unobserved, were measured on a four-angle automated diffractometer, using monochromatic copper radiation. The structure was solved by direct methods, using the program MULTAN, and was refined by the least-squares method. The final R factor was 0.077 with anisotropic temperature factors for the heavy atoms and isotropic temperature factors for the hydrogen atoms, which were placed at assumed positions. The atomic coordinates and temperature factors (Table IV) and the bond distances and bond angles (Table V) are included in the supplementary material.

***trans*-(±)-7-Acetyl-2,3,4,4a,5,7,9,9a-octahydro-1-methyl-1*H*-pyrrolo[3,4-*g*]quinoline (24; R = Me) Maleate Salt.** A solution of 975 mg (13 mmol) of glycine and 730 mg (13 mmol) of KOH was prepared in 100 mL of absolute EtOH. The enamino ketone **23** (R = Me), 2.8 g (12.6 mmol), was added, and the mixture was heated under reflux for 3 h. The solution was concentrated, Et_2O was added, and the potassium salt adduct was filtered: yield 3.5 g. It was added to 100 mL of Ac_2O, and the resulting mixture was heated under reflux for 45 min. Excess Ac_2O was distilled in vacuo, and the residue was taken up in CH_2Cl_2 and filtered. The solvent was distilled, and the crude product was purified by chromatography twice on Florisil: yield 1.72 g. The maleate salt was prepared in MeOH–Et_2O: yield 2 g (45%). It was recrystallized from the same solvent mixture: yield 1.23 g; mp 201–203 °C dec. Anal. ($C_{18}H_{24}N_2O_5$) C, H, N.

***trans*-(±)-2,3,4,4a,5,7,9,9a-Octahydro-1-methyl-1*H*-pyrrolo[3,4-*g*]quinoline (25; R = Me) and Its Maleate Salt.** The maleate salt of the *N*-acetyl compound **24** (R = Me), 1.2 g (3.4 mmol), was hydrolyzed in 100 mL of MeOH and 10 mL of 2 N NaOH by stirring the solution under reflux, under N_2, for 35 min. The mixture was diluted with H_2O–NaOH, and the product was extracted well with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and evaporated: yield 400 mg (62%). The product was purified by chromatography on Florisil. Part was characterized as the free base, mp 200–202 °C dec from ether. Anal. ($C_{12}H_{18}N_2$) C, H, N. Part was converted to the maleate salt, mp 205 °C dec from MeOH–Et_2O. Anal. ($C_{16}H_{22}N_2O_4$) C, H, N.

6-(Benzoyloxy)-3-carbethoxy-1-propyl-1,2,3,4,5,6,7,8-octahydroquinoline (28). In the synthetic sequence **20** → **28** → **29** → **30** → **31** → **32** → **33**, the intermediates were noncrystalline. However, each was shown to be homogeneous by TLC and was characterized by IR, NMR, etc. before use in the next reaction.

A solution of 2.0 mL of propylamine (24 mmol) in 100 mL of toluene was cooled in ice. To it was added dropwise a solution of 2.3 g of ethyl α-bromomethylacrylate[31] (12 mmol) in 25 mL of toluene. Stirring at 0 °C was continued for 15 min, after which a mixture of 2.2 g (10 mmol) of *p*-(benzoyloxy)cyclohexanone[22]

(31) A. F. Ferris, *J. Org. Chem.*, **20**, 780 (1955).

in 40 mL of toluene was added. The resulting solution was then heated under reflux under N_2 for 17 h under a Dean–Stark trap containing 5 Å molecular seive. The mixture was cooled and evaporated in vacuo. The crude product was purified by chromatography on Florisil using $CHCl_3$–4% MeOH as eluant; the yield of the major fraction was 2.2 g (60%). The oily product was used without further purification.

***trans*-(±)-6-(Benzoyloxy)-3-carbethoxy-1-propyldecahydroquinoline (29).** Diester **28**, 2.2 g (6 mmol), was dissolved in 100 mL of Et_2O, and the hydrochloride was precipitated using dry HCl. The supernatant was decanted and discarded. The residual salt was dissolved in 25 mL of MeOH, and 75 mL of THF was added. The solution was cooled in ice, and 2 g of $NaCNBH_3$ (0.0318 mol) was added in portions with stirring. Stirring and cooling was continued for 1.5 h. Aqueous $NaHCO_3$ was added, and the product was extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and concentrated. Purification was effected by chromatography on 35 g of Florisil: oil; yield 1.4 g (64%).

***trans*-(±)-3-Carbethoxy-1-propyldecahydro-6-quinolinol (30).** The diester **29** (1.4 g, 3.6 mmol) was dissolved in 25 mL of THF and 25 mL of MeOH. NaOH, 2 N (15 mL), was added, and the solution was stirred at 25 °C for 3.25 h. The solvents were distilled, and 50 mL of H_2O was added to the residue. The resulting solution was saturated with CO_2, washed several times with $CHCl_3$–*i*-PrOH, and evaporated to dryness in vacuo at 80 °C. The residue was dissolved in 200 mL of EtOH. Concentrated HCl (3 mL) was added, and the solution was heated under reflux for 22.5 h under a Soxhlet extractor containing 3 Å molecular sieve. Aqueous $NaHCO_3$ was added, and the mixture was extracted several times with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The crude product was purified by chromatography on 30 g of Florisil using $CHCl_3$–2% MeOH as eluant; a thick oil was obtained: yield 0.52 g (52%).

***trans*-(±)-Octahydro-3-carbethoxy-1-propyl-6(2*H*)-quinolinone (31).** The monoester alcohol **30** (5.2 g, 19.3 mmol) was dissolved in 300 mL of CH_2Cl_2, and 2.5 g (30 mmol) of NaOAc was added followed by 6.5 g (30 mmol) of pyridine hydrochloride chromate. The mixture was stirred for 15.5 h at 25 °C under N_2, filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography on 150 g of Florisil using $CHCl_3$/1–2% MeOH as eluant; yield, 3.1 g (60%).

***trans*-(±)-3-Carbethoxy-7-[(dimethylamino)methylene]-1-propyloctahydro-6(2*H*)-quinolinone (32).** A solution of 3.1 g (1.16 mmol) of the keto ester **31** in 25 mL of DMF dimethyl acetal and 75 mL of toluene was heated under reflux under N_2 for 43 h. Volatiles were distilled, and the product was purified by chromatography twice on 150 g of Florisil using $CHCl_3$/0–5% MeOH as eluant: yield 2.3 g (60%).

(3β,4aα,9aβ)-(±)-2,3,4,4a,5,7,9,9a-Octahydro-7-acetyl-3-carbethoxy-1-propyl-1*H*-pyrrolo[3,4-*g*]quinoline (33). Potassium glycinate was prepared using 280 mg (5 mmol) of KOH and 370 mg (5 mmol) of glycine in 50 mL of EtOH. The enamino ketone **32** (1.3 g, 4 mmol) was added, and the solution was heated under reflux for 3 h under N_2. The mixture was concentrated to dryness in vacuo, and a solution of the residue in 50 mL of Ac_2O was heated under reflux for 45 min. Solvents were distilled, aqueous $NaHCO_3$ was added, and the product was extracted with $CHCl_3$. The extract was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated. The product was purified by chromatography on 35 g of Florisil using $CHCl_3$/0–1% MeOH as eluant: yield 0.45 g. The maleate salt was prepared in ether and was recrystallized from MeOH–Et_2O: yield 280 mg (15%); mp 179–180 °C. Anal. ($C_{23}H_{32}N_2O_7$) C, H, N.

(3β,4aα,9aβ)-(±)-2,3,4,4a,5,7,9,9a-Octahydro-3-carbethoxy-1-propyl-1*H*-pyrrolo[3,4-*g*]quinoline (34). The *N*-acetyl ester **33** (690 mg, 2.08 mmol) was treated with a solution of excess NaOEt in EtOH for 0.5 h at 25 °C. The solution was diluted with H_2O and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The product was recrystallized from EtOH: yield 130 mg (29%); mp 163–164 °C. Anal. ($C_{17}H_{26}N_2O_2$) C, H, N.

(3β,4aα,9aβ)-(±)-2,3,4,4a,5,7,9,9a-Octahydro-1-propyl-1*H*-pyrrolo[3,4-*g*]quinoline-3-methanol (35). A solution of ester **34** (0.5 g, 1.72 mmol) in 75 mL of THF was treated in portions with 1.0 g of $LiAlH_4$. Stirring was continued for 2.25 h, after which excess reagent was decomposed with EtOAc and 10% NaOH. The mixture was diluted with H_2O and extracted well with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated. The product was recrystallized from EtOAc–Et_2O: mp 178–180 °C; yield 400 mg (94%). Anal. ($C_{15}H_{24}N_2O$) C, H, N.

5-Acetamido-4,5,6,7-tetrahydroindazole (36) Methanesulfonic Acid Salt. A solution of the enamino ketone **18** (1.46 g, 7.0 mmol) and 0.35 mL of $H_2NNH_2 \cdot H_2O$ (7.0 mmol) in 25 mL of MeOH was stirred at 25 °C for 16 h. The solvent was evaporated, and the product was purified by chromatography on Florisil using $CHCl_3$/2–5% MeOH as eluant. The base was converted to the methanesulfonic acid salt using 0.5 mL of CH_3SO_3H in EtOH: yield 1.61 g (84%): mp 190–192 °C. Anal. ($C_{10}H_{17}N_3O_4S$) C, H, N, S.

5-Amino-4,5,6,7-tetrahydroindazole (37; R = H) Dihydrochloride. A solution of 950 mg (3.46 mmol) of the amide **36** mesylate salt in 50 mL of 6 N HCl was heated under reflux under N_2 for 4.5 h. It was then concentrated, and the product was crystallized from EtOH: yield 585 mg (80%); mp 260–280 °C. Anal. ($C_7H_{13}Cl_2N_3$) C, H, N, Cl.

5-(Dimethylamino)-4,5,6,7-tetrahydroindazole (37; R = Me) Dihydrochloride. The primary amine **37** (R = H) dihydrochloride (630 mg, 3 mmol) and 410 mg (5 mmol) of NaOAc were dissolved in 75 mL of MeOH. To the solution was then added 380 mg (6 mmol) of $NaCNBH_3$ and 1.0 mL (20 mmol) of 37% aqueous formaldehyde. Stirring was maintained at 25 °C for 17 h, after which the solution was poured into cold, dilute HCl. The mixture was washed with $CHCl_3$, and the aqueous layer was made basic with NH_4OH. The mixture was extracted several times with $CHCl_3$–*i*-PrOH, and the extract was washed with brine, dried (Na_2SO_4), and evaporated. The base was converted to the dihydrochloride salt using HCl, and the salt was crystallized from EtOH: yield 430 mg (63%); mp 220–228 °C. Anal. ($C_9H_{17}Cl_2N_3$) C, H, N.

5-(Dipropylamino)-4,5,6,7-tetrahydroindazole (37; R = Pr) Dihydrochloride. This compound was prepared from **37** (R = H) using propionaldehyde and $NaCNBH_3$ as above: yield 98%; mp 154–160 °C. Anal. ($C_{13}H_{25}Cl_2N_3$) C, H, N.

***trans*-(±)-Octahydro-1-cyano-6(2*H*)-quinolinone (22; R = CN).** A solution of 53 g (0.216 mol) of *trans*-(±)-1-benzyl-6-hydroxydecahydroquinoline in 1.5 L of CH_2Cl_2 was cooled in ice. Cyanogen bromide (50 g, 0.47 mol) was added, and the mixture was stirred at 25 °C for 15 h. The solution was washed with 1 N HCl and with H_2O, dried (Na_2SO_4), and evaporated. The *trans*-(±)-1-cyano-6-hydroxydecahydroquinoline was purified by chromatography on 300 g of Florisil using $CHCl_3$/0–2% MeOH as eluant: yield 22.5 g (58%). The starting 1-benzyl compound (11 g, 20%) was recovered from the acid wash. The 1-cyano compound (22.5 g, 0.125 mol) was dissolved in 1200 mL of CH_2Cl_2. To the solution was then added 43 g (0.2 mol) of pyridine hydrochloride chromate and stirring under N_2 was continued for 6 h. The mixture was filtered, and the filtrate was concentrated in vacuo. The ketone product was purified by chromatography on 300 g of Florisil using $CHCl_3$–1% MeOH as eluant: yield 18.9 g (84%); mp 86–88 °C from Et_2O–$CHCl_3$. Anal. ($C_{10}H_{14}N_2O$) C, H, N.

***trans*-(±)-1-Cyano-7-[(dimethylamino)methylene]octahydro-6(2*H*)-quinolinone (23; R = CN).** A solution of ketone **22** (R = CN), 16.7 g (0.094 mol), 50 g of DMF dimethyl acetal, and 200 mL of toluene was heated under reflux for 19 h. It was then concentrated in vacuo, and the product was purified by chromatography on 150 g of Florisil: yield 12.6 g (58%); mp 150–157 °C. A sample was recrystallized from toluene, mp 162–164 °C. Anal. ($C_{13}H_{19}N_3O$) C, H, N.

***trans*-(±)-4,4a,5,6,7,8,8a,9-Octahydro-5-cyano-2*H*-pyrazolo[3,4-*g*]quinoline (38; R = CN).** A solution of 6.5 g (28 mmol) of the enamino ketone **23** (R = CN) and 1.7 mL (30 mmol) of $H_2NNH_2 \cdot H_2O$ in 300 mL of MeOH was stirred at 25 °C for 15.5 h. The solvent was evaporated, and the product was purified by chromatography on 150 g of Florisil using $CHCl_3$/2–5% MeOH as eluant: yield 3.31 g (58%); mp 193–195 °C from EtOH. Anal. ($C_{11}H_{14}N_4$) C, H, N.

***trans*-(±)-4,4a,5,6,7,8,8a,9-Octahydro-2*H*-pyrazolo[3,4-*g*]quinoline (38; R = H) Dihydrochloride.** A suspension of 860 mg (4.26 mmol) of the *N*-cyano compound **38** (R = CN) and 5 g of zinc dust in 50 mL of HOAc and 10 mL of H_2O was heated

under reflux under N_2 for 18.5 h. It was then filtered, and the filtrate was poured onto ice and made basic with NH_4OH. The mixture was extracted with $CHCl_3$–*i*-PrOH, and the extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was converted to the dihydrochloride salt using concentrated HCl in EtOH: yield 780 mg (73%); mp 284–287 °C. Anal. ($C_{10}H_{17}Cl_2N_3$) C, H, N, Cl.

***trans*-(±)-4,4a,5,6,7,8,8a,9-Octahydro-5-methyl-2*H*-pyrazolo[3,4-*g*]quinoline (38; R = Me) Dihydrochloride.** The enamino ketone **23** (R = Me) was converted to the pyrazole **38** (R = Me) as above for **23** (R = CN). The yield of the dihydrochloride salt was 67%, mp 268–270 °C dec from EtOH. Anal. ($C_{11}H_{19}Cl_2N_3$) C, H, N, Cl.

***trans*-(±)-4,4a,5,6,7,8,8a,9-Octahydro-5-propyl-2*H*-pyrazolo[3,4-*g*]quinoline (38; R = Pr) Dihydrochloride.** Crude secondary amine **38** (R = H) from 6.3 g (31 mmol) of *N*-cyanoamine **38** (R = CN) was dissolved in 500 mL of MeOH. $NaCNBH_3$, 1.9 g (30 mmol), and 20 mL of CH_3CH_2CHO were added, and the solution was stirred under N_2 for 28 h. The mixture was poured into 1 N HCl, and the acidic solution was washed with Et_2O. The aqueous layer was made basic with NH_4OH and was then extracted well with $CHCl_3$–*i*-PrOH. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The base **38** (R = Pr) was converted to the dihydrochloride salt using concentrated HCl in acetone: yield 4.6 g (51%); mp 250–257 °C. Anal. ($C_{13}H_{23}Cl_2N_3$) C, H, N, Cl.

***trans*-(±)-4,4a,5,6,7,8,8a,9-Octahydro-5-allyl-2*H*-pyrazolo[3,4-*g*]quinoline (38; R = Allyl) Dihydrochloride.** This derivative was made by the procedure used with **38** (R = Me). The sequence was: **21** (R = H) → **21** (R = allyl) → **22** (R = allyl) → **23** (R = allyl) → **38** (R = allyl). Each intermediate was purified by chromatography on Florisil, and the yields were comparable. **38**·2HCl (R = allyl) had mp 215 °C dec from acetone. Anal. ($C_{13}H_{21}Cl_2N_3$) C, H, N, Cl.

(4a*β*,7*β*,8a*α*)-(±)-4,4a,5,6,7,8,8a,9-Octahydro-7-carbethoxy-5-propyl-2*H*-pyrazolo[3,4-*g*]quinoline (39; R = Pr). The enamino ketone **32** with hydrazine at 25 °C gave the pyrazole ester **39** (R = Pr) as above: yield 75%; a portion was crystallized from Et_2O–hexane, mp 125–127 °C. Anal. ($C_{16}H_{25}N_3O_2$) C, H, N.

(4a*β*,7*β*,8a*α*)-(±)-4,4a,5,6,7,8,8a,9-Octahydro-5-propyl-2*H*-pyrazolo[3,4-*g*]quinoline-7-methanol. A solution of 1.55 g (5.3 mmol) of ester **39** (R = Pr) in 150 mL of THF was treated in portions with 1 g of $LiAlH_4$. The mixture was stirred at 25 °C for 18 h and cooled, and excess hydride was decomposed with EtOH and 10% NaOH. Water was added, and the resulting mixture was extracted several times with $CHCl_3$–*i*-PrOH. The extract was washed with brine, dried (Na_2SO_4), and evaporated: yield 0.95 g (69%). A portion was crystallized from $CHCl_3$–EtOH, mp 167–169 °C. Anal. ($C_{14}H_{23}N_3O$) C, H, N.

(4a*β*,7*β*,8a*α*)-(±)-4,4a,5,6,7,8,8a,9-Octahydro-2-(methanesulfonyl)-7-[[(methanesulfonyl)oxy]methyl]-5-propyl-2*H*-pyrazolo[3,4-*g*]quinoline. A solution of 0.64 g (2.57 mmol) of the alcohol above and 1 mL of methanesulfonyl chloride in 50 mL of pyridine was stirred at 25 °C under N_2 for 23 h. It was then diluted with H_2O and extracted well with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and evaporated: yield 0.71 g (68%). A portion was crystallized from Et_2O, mp 152–154 °C. Anal. ($C_{16}H_{27}N_3O_5S_2$) C, H, N, S.

(4a*β*,7*β*,8a*α*)-(±)-4,4a,5,6,7,8,8a,9-Octahydro-7-[(methylthio)methyl]-5-propyl-2*H*-pyrazolo[3,4-*g*]quinoline (40; R = Pr) and Its Dihydrochloride Salt. A solution of 2 g of CH_3SH (40 mmol) in 60 mL of DMF was cooled in ice, and to it was added in portions 1.9 g of NaH (50% in mineral oil, 40 mmol). The cooling bath was removed, and to the solution was added slowly 0.71 g (1.7 mmol) of the above dimethanesulfonyl derivative in 25 mL of DMF. Stirring at 25 °C under N_2 was continued for 4.5 h. The solution was diluted with H_2O and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography on 30 g of Florisil using $CHCl_3$/2–4% MeOH as eluant: yield 0.32 g (60%). A portion was crystallized from Et_2O, mp 135–137 °C. Anal. ($C_{15}H_{25}N_3S$) C, H, N, S. The dihydrochloride salt was prepared in acetone–MeOH: mp 185 °C dec. Anal. ($C_{15}H_{27}Cl_2N_3S$) C, H, N, Cl.

6-Ethoxy-4,5-dihydroindazole (43). A solution of 5.45 g (32 mmol) of the formyl ketone **42**[29] in 150 mL of EtOH was treated with 1.9 mL (35 mmol) of $H_2NNH_2 \cdot H_2O$. The mixture was stirred at 25 °C for 18 h, after which it was evaporated in vacuo. The crude product was purified by chromatography on 100 g of Florisil using $CHCl_3$/1–2% EtOH as eluant: yield 3.64 g (67%). A sample was recrystallized from Et_2O–hexane, mp 118–120 °C. Anal. ($C_9H_{12}N_2O$) C, H, N.

2,4,5,7-Tetrahydro-6*H*-indazol-6-one (44) Methanesulfonic Acid Salt. A solution of 3.2 g (19.6 mmol) of the enol ether **43** in 150 mL of 1 N HCl was stirred at 25 °C under N_2 for 1.25 h. Excess $NaHCO_3$ was added, and the mixture was extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The product was purified by filtration of a solution of it in $CHCl_3$–2% MeOH through 30 g of Florisil: yield 1.5 g (56%). The methanesulfonic acid salt was prepared in EtOH–Et_2O, mp 95–105 °C. Anal. ($C_8H_{12}N_2O_4S$) C, H, N, S.

6-Amino-4,5,6,7-tetrahydroindazole (45) Dihydrochloride. A solution of 1.5 g (6.5 mmol) of the ketone **44** methanesulfonate salt, 5.4 g (0.07 mol) of NH_4OAc, and 410 mg (6.5 mmol) of $NaCNBH_3$ in 150 mL of MeOH was stirred at 25 °C under N_2 for 22 h. The mixture was poured into 10% NaOH, and the product was extracted with several portions of $CHCl_3$–*i*-PrOH. The extracts were washed with brine, dried (Na_2SO_4), and evaporated. The base was converted to the dihydrochloride salt using HCl in aqueous EtOH: yield 590 mg (32%); mp 275–280 °C. Anal. ($C_7H_{13}Cl_2N_3$) C, H, N.

6-(Dipropylamino)-4,5,6,7-tetrahydroindazole (46). The crude primary amine **45** (0.7 g, 5.1 mmol) in 100 mL of MeOH was treated with 3 mL of propionaldehyde (0.04 mol) and 0.5 g (0.08 mol) of $NaCNBH_3$. The resulting solution was stirred for 20 h, after which it was poured into 1 N HCl. The mixture was washed with ether, and the acid layer was made basic with NaOH. The product was extracted into $CHCl_3$–*i*-PrOH, and the extract was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography on 30 g of Florisil using $CHCl_3$/1–10% MeOH as eluant. The purified product, though noncrystalline, was homogeneous by TLC: MS showed a strong molecular ion at 221 ($C_{13}H_{23}N_3$); yield 70 mg (6.2%).

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Supplementary Material Available: Table IV, atomic coordinates and U_{ij} values; Table V, bond distances and bond angles pertaining to the X-ray structure determination of compound **23** (R = Me) (2 pages). Ordering information is given in any current masthead page.